

Appl. No. : 09/811,901
Filed : March 19, 2001

AMENDMENTS TO THE CLAIMS

Please cancel claims 1, and 129-138.

Claims 1-138. (Cancelled)

139. (Previously presented) A method for encapsulation of at least one islet cell encapsulated in a microcapsule, comprising the steps of:

- a) coating at least one islet cell encapsulated in a microcapsule with photoinitiator;
- b) suspending the at least one coated islet cell encapsulated in a microcapsule in a macromer solution comprised of macromer; and
- c) irradiating the suspension with light.

140. (Previously presented) The method of claim 139, wherein the macromer is a water soluble, ethylenically unsaturated, polymer susceptible to polymerization into water insoluble polymer through interaction of at least two carbon-carbon double bonds.

141. (Previously presented) The method of claim 140, wherein the macromer is selected from the group consisting of ethylenically unsaturated derivatives of poly(ethylene oxide) (PEO), poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP), poly(ethyloxazoline) (PEOX), poly(amino acids), polysaccharides, and proteins.

142. (Previously presented) The method of claim 141, wherein the polysaccharides are selected from the group consisting of alginate, hyaluronic acid, chondroitin sulfate, dextran, dextran sulfate, heparin, heparin sulfate, heparan sulfate, chitosan, gellan gum, xanthan gum, guar gum, water soluble cellulose derivatives and carrageenan.

143. (Previously presented) The method of claim 141, wherein the proteins are selected from the group consisting of gelatin, collagen, and albumin.

144. (Previously presented) The method of claim 139, wherein the photoinitiator is any dye that absorbs light having a frequency between 320 nm and 900 nm, can form free radicals, is

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at least partially water soluble, and is non-toxic to the at least one islet cell at the concentration used for polymerization.

145. (Previously presented) The method of claim 139, wherein the macromer solution further comprises a primary, secondary, tertiary, or quaternary amine cocatalyst and the photoinitiator is selected from the group of ethyl eosin, eosin Y, fluorescein, 2, 2-dimethoxy, 2-phenylacetophenone, 2-methyl, 2-phenylacetophenone, camphorquinone, rose bengal, methylene blue, erythrosin, phloxime, thionine, riboflavin, and methyl green.

146. (Previously presented) The method of claim 139, wherein the microcapsule is comprised of material selected from the group of alginate, chitosan, agarose, and gelatin.

147. (Previously presented) The method of claim 139, wherein the macromer solution further comprises an accelerator to increase the rate of polymerization.

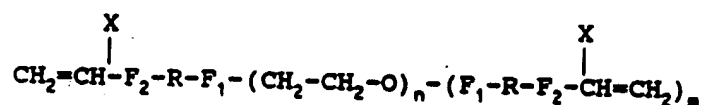
WE CLAIM:

1. A method for encapsulation of biological material comprising the steps of
 - a) mixing the biological material in an aqueous macromer solution comprising macromer and photoinitiator;
 - b) forming small globular geometric shapes of the mix in (a); and
 - c) polymerizing the macromer by exposing the geometric shapes to light radiation.
2. The method of claim 1 wherein the macromer is a water soluble, ethylenically unsaturated, polymer susceptible to polymerization into an water insoluble polymer through interaction of at least two carbon-carbon double bonds.
3. The method of claim 2 wherein the macromer is selected from the group consisting of ethylenically unsaturated derivatives of poly(ethylene oxide) (PEO), poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP), poly(ethyloxazoline) (PEOX), poly(amino acids), polysaccharides, and proteins.
4. The method of claim 3 wherein the PEG is PEG multiacrylate.
5. The method of claim 4 wherein the PEG is PEG tetraacrylate which has a molecular weight around 18,500 D.

6. The method of claim 3 wherein the polysaccharides are selected from the group consisting of alginate, hyaluronic acid, chondroitin sulfate, dextran, dextran sulfate, heparin, heparin sulfate, heparan sulfate, chitosan, gellan gum, xanthan gum, guar gum, water soluble cellulose derivatives and carrageenan.

7. The method of claim 3 wherein the proteins are selected from the group consisting of gelatin, collagen and albumin.

8. The method of claim 1 wherein the macromer is of the formula



where $\text{F}_1 = \text{CONH}, \text{COO}$ or NHCOO

$\text{X} = \text{H}, \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5, \text{Cl}, \text{Br}, \text{OH}$ or CH_2COOH

$\text{F}_2 = \text{COO}, \text{CONH}, \text{O}$ or C_6H_4 ,

$\text{R} = \text{CH}_2$ or $-\text{alkyl}-$,

$n \geq 5$, and

$m \geq 2$.

9. The method of claim 1 wherein the photoinitiator is any dye which absorbs light having frequency between 320 nm and 900 nm, can form free radicals, is at least partially water soluble, and is non-toxic to the biological material at the concentration used for polymerization.

10. The method of claim 9 wherein the photoinitiator is selected from the group consisting of 2,2-dimethoxy,2-phenylacetophenone and 2-methoxy,2-phenylacetophenone.
11. The method of claim 1 wherein the macromer solution further comprises a cocatalyst and the photoinitiator is selected from the group consisting of ethyl eosin, eosin Y, fluorescein, 2,2-dimethoxy,2-phenylacetophenone, 2-methoxy,2-phenylacetophenone, camphorquinone, rose bengal, methylene blue, erythrosin, phloxime, thionine, riboflavin and methylene green.
12. The method of claim 11 wherein the cocatalyst is a nitrogen based compound capable of stimulating a free radical reaction.
13. The method of claim 11 wherein the cocatalyst is a nitrogen atom-containing electron-rich molecule.
14. The method of claim 11 wherein the cocatalyst is a primary, secondary, tertiary or quaternary amine.
15. The method of claim 14 wherein the cocatalyst is selected from the group consisting of triethanolamine, triethylamine, ethanolamine, N-methyl diethanolamine, N,N-dimethyl benzylamine, dibenzyl amine, N-benzyl ethanolamine, N-isopropyl benzylamine, tetramethyl ethylenediamine, potassium persulfate, tetramethyl ethylenediamine, lysine, ornithine, histidine and arginine.

16. The method of claim 1 wherein the radiation has a wavelength between 320 nm and 900 nm.
17. The method of claim 16 wherein the radiation has a wavelength between 350 nm and 700 nm.
18. The method of claim 1 wherein the biological material is selected from mammalian tissue, mammalian cells, sub-cellular organelles and sub-cellular non-organelle components.
19. The method of claim 18 wherein the cells are primary cells or established cell lines.
20. The method of claim 18 wherein the biological material is selected from pancreatic islet cells, human foreskin fibroblasts, Chinese hamster ovary cells, beta cell insulomas, lymphoblastic leukemia cells, mouse 3T3 fibroblasts, dopamine secreting ventral mesencephalon cells, neuroblastoid cells, adrenal medulla cells, and T-cells.
21. The method of claim 1 wherein the biological material is selected from proteins, polysaccharides, oligonucleotides, enzymes, enzyme systems, bacteria, microbes, vitamins, cofactors, blood clotting factors, drugs, immunogens, hormones, and retroviruses.
22. The method of claim 21 wherein the protein is hemoglobin.

23. The method of claim 21 wherein the enzyme is adenosine deaminase.

24. The method of claim 21 wherein the drugs are selected from TPA, streptokinase and heparin.

25. The method of claim 1 wherein the geometric shapes are formed by coextrusion of the aqueous macromer solution mixed with the biological material with a non-toxic, non-immunogenic, non-miscible substance capable of maintaining droplet formation.

26. The method of claim 25 wherein the non-miscible substance is oil

27. The method of claim 26 wherein the oil is mineral oil.

28. The method of claim 1 wherein the geometric shapes are formed by coextrusion of the aqueous macromer solution mixed with the biological material in air.

29. The method of claim 1 wherein the geometric shapes are formed by agitation of the aqueous macromer solution mixed with the biological material with a non-toxic, non-immunogenic, non-miscible substance.

30. The method of claim 29 wherein the non-miscible substance is oil.

31. The method of claim 1 wherein the biological material is first encapsulated in a microcapsule.
32. The method of claim 31 wherein the microcapsule is comprised of ionically coagulatable or thermally coagulatable polymers which are non-toxic to the encapsulated material.
33. The method of claim 32 wherein the microcapsule is comprised of alginate.
34. The method of claim 32 wherein the microcapsule is comprised of chitosan.
35. The method of claim 32 wherein the microcapsule is comprised of agarose.
36. The method of claim 32 wherein the microcapsule is comprised of gelatin.
37. The method of claim 1 wherein the macromer solution further comprises an accelerator to accelerate the rate of polymerization.
38. The method of claim 37 wherein the accelerator is a small molecule containing an allyl, vinyl or acrylate group.
39. The method of claim 38 wherein the accelerator is selected from the group consisting of N-vinyl pyrrolidinone, 2-vinyl pyridine, 1-vinyl imidazole, 9-vinyl carbazole, acrylic acid and 2-allyl,2-methyl,1-3-cyclopentane dione.

40. The method of claim 39 wherein the accelerator is N-vinyl pyrrolidinone.

41. A method for encapsulation of biological material comprising the steps of

- a) coating the biological material with photoinitiator;
- b) suspending the coated material in a macromer solution comprised of macromer; and
- c) irradiating the suspension with light.

42. The method of claim 41 wherein the macromer is a water soluble, ethylenically unsaturated, polymer susceptible to polymerization into an water insoluble polymer through interaction of at least two carbon-carbon double bonds.

43. The method of claim 42 wherein the macromer is selected from the group consisting of ethylenically unsaturated derivatives of poly(ethylene oxide) (PEO), poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP), poly(ethyloxazoline) (PEOX), poly(amino acids), polysaccharides, and proteins.

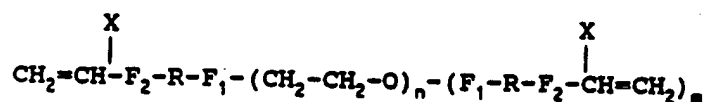
44. The method of claim 43 wherein the PEG is PEG multiacrylate.

45. The method of claim 44 wherein the PEG is PEG tetraacrylate which has a molecular weight around 18,500 D.

46. The method of claim 43 wherein the polysaccharides are selected from the group consisting of alginate, hyaluronic acid, chondroitin sulfate, dextran, dextran sulfate, heparin, heparin sulfate, heparan sulfate, chitosan, gellan gum, xanthan gum, guar gum, water soluble cellulose derivatives and carrageenan.

47. The method of claim 43 wherein the proteins are selected from the group consisting of gelatin, collagen and albumin.

48. The method of claim 41 wherein the macromer is of the formula



where $\text{F}_1 = \text{CONH}, \text{COO}$ or NHCOO

$\text{X} = \text{H}, \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5, \text{Cl}, \text{Br}, \text{OH}$ or CH_2COOH

$\text{F}_2 = \text{COO}, \text{CONH}, \text{O}$ or C_6H_4 ,

$\text{R} = \text{CH}_2$ or $-\text{alkyl}-$,

$n \geq 5$, and

$m \geq 2$.

49. The method of claim 41 wherein the photoinitiator is any dye which absorbs light having frequency between 320 nm and 900 nm, can form free radicals, is at least partially water soluble, and is non-toxic to the biological material at the concentration used for polymerization.

50. The method of claim 49 wherein the photoinitiator is selected from the group consisting of 2,2-dimethoxy,2-phenylacetophenone and 2-methoxy,2-phenylacetophenone.

51. The method of claim 41 wherein the macromer solution further comprises a cocatalyst and the photoinitiator is selected from the group consisting of ethyl eosin, eosin Y, fluorescein, 2,2-dimethoxy,2-phenylacetophenone, 2-methoxy,2-phenylacetophenone, camphorquinone, rose bengal, methylene blue, erythrosin, phloxime, thionine, riboflavin and methylene green.

52. The method of claim 51 wherein the cocatalyst is a nitrogen based compound capable of stimulating a free radical reaction.

53. The method of claim 51 wherein the cocatalyst is a a nitrogen atom-containing electron-rich molecule.

54. The method of claim 51 wherein the cocatalyst is a primary, secondary, tertiary or quaternary amine.

55. The method of claim 54 wherein the cocatalyst is selected from the group consisting of triethanolamine, triethylamine, ethanolamine, N-methyl diethanolamine, N,N-dimethyl benzylamine, dibenzyl amine, N-benzyl ethanolamine, N-isopropyl benzylamine, tetramethyl ethylenediamine, potassium persulfate, tetramethyl ethylenediamine, lysine, ornithine, histidine and arginine.

56. The method of claim 41 wherein the radiation has a wavelength between 320 nm and 900 nm.
57. The method of claim 56 wherein the radiation has a wavelength between 350 nm and 700 nm.
58. The method of claim 41 wherein the biological material is selected from mammalian tissue, mammalian cells, sub-cellular organelles and sub-cellular non-organelle components.
59. The method of claim 58 wherein the cells are primary cells or established cell lines.
60. The method of claim 58 wherein the biological material is selected from pancreatic islet cells, human foreskin fibroblasts, Chinese hamster ovary cells, beta cell insulomas, lymphoblastic leukemia cells, mouse 3T3 fibroblasts, dopamine secreting ventral mesencephalon cells, neuroblastoid cells, adrenal medulla cells, and T-cells.
61. The method of claim 41 wherein the biological material is selected from proteins, polysaccharides, oligonucleotides, enzymes, enzyme systems, bacteria, microbes, vitamins, cofactors, blood clotting factors, drugs, immunogens, hormones, and retroviruses.
62. The method of claim 61 wherein the protein is hemoglobin.

63. The method of claim 61 wherein the enzyme is adenosine deaminase.

64. The method of claim 61 wherein the drugs are selected from TPA, streptokinase and heparin.

65. The method of claim 41 wherein the geometric shapes are formed by coextrusion of the aqueous macromer solution mixed with the biological material with a non-toxic, non-immunogenic, non-miscible substance capable of maintaining droplet formation.

66. The method of claim 65 wherein the non-miscible substance is oil.

67. The method of claim 66 wherein the oil is mineral oil.

68. The method of claim 41 wherein the geometric shapes are formed by coextrusion of the aqueous macromer solution mixed with the biological material in air.

69. The method of claim 41 wherein the geometric shapes are formed by agitation of the aqueous macromer solution mixed with the biological material with a non-toxic, non-immunogenic, non-miscible substance.

70. The method of claim 69 wherein the non-miscible substance is oil.

71. The method of claim 41 wherein the biological material is first encapsulated in a microcapsule.

72. The method of claim 71 wherein the microcapsule is comprised of ionically coagulatable or thermally coagulatable polymers which are non-toxic to the encapsulated material.

73. The method of claim 72 wherein the microcapsule is comprised of alginate.

74. The method of claim 72 wherein the microcapsule is comprised of chitosan.

75. The method of claim 72 wherein the microcapsule is comprised of agarose.

76. The method of claim 72 wherein the microcapsule is comprised of gelatin.

77. The method of claim 41 wherein the macromer solution further comprises an accelerator to accelerate the rate of polymerization.

78. The method of claim 77 wherein the accelerator is a small molecule containing an allyl, vinyl or acrylate group.

79. The method of claim 78 wherein the accelerator is selected from the group consisting of N-vinyl pyrrolidinone, 2-vinyl pyridine, 1-vinyl imidazole, 9-vinyl carbazole, acrylic acid and 2-allyl,2-methyl,1-3-cyclopentane dione.

80. The method of claim 79 wherein the accelerator is N-vinyl pyrrolidinone.

81. A method of applying a biocompatible surface to a biomedical device having a polymeric surface which can be at least partly swelled comprising the steps of:

- (a) swelling the polymeric surface in a solvent;
- (b) applying a macromer solution, comprised of macromer, to the surface;
- (c) irradiating the macromer solution to initiate polymerization; and
- (d) deswelling the polymeric surface by removing it from the solvent.

82. The method of claim 81 wherein the macromer is a water soluble, ethylenically unsaturated, polymer susceptible to polymerization into an water insoluble polymer through interaction of at least two carbon-carbon double bonds.

83. The method of claim 82 wherein the macromer is selected from the group consisting of ethylenically unsaturated derivatives of poly(ethylene oxide) (PEO), poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP), poly(ethyloxazoline) (PEOX), poly(amino acids), polysaccharides, and proteins.

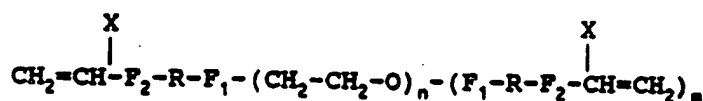
84. The method of claim 83 wherein the PEG is PEG multiacrylate.

85. The method of claim 84 wherein the PEG is PEG tetraacrylate which has a molecular weight around 18,500 D

86. The method of claim 83 wherein the polysaccharides are selected from the group consisting of alginate, hyaluronic acid, chondroitin sulfate, dextran, dextran sulfate, heparin, heparin sulfate, heparan sulfate, chitosan, gellan gum, xanthan gum, guar gum, water soluble cellulose derivatives and carrageenan.

87. The method of claim 83 wherein the proteins are selected from the group consisting of gelatin, collagen and albumin.

88. The method of claim 81 wherein the macromer is of the formula



where $\text{F}_1 = \text{CONH}, \text{COO}$ or NHCOO

$\text{X} = \text{H}, \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5, \text{Cl}, \text{Br}, \text{OH}$ or CH_2COOH

$\text{F}_2 = \text{COO}, \text{CONH}, \text{O}$ or C_6H_4 ,

$\text{R} = \text{CH}_2$ or $-\text{alkyl}-$,

$n \geq 5$, and

$m \geq 2$.

89. The method of claim 81 wherein polymerization is initiated by gamma ray or electron beam radiation.

90. The method of claim 81 wherein the macromer solution further comprises a photoinitiator, and polymerization is initiated by light having wavelength of 320-900 nm.

91. The method of claim 90 wherein the photoinitiator is any dye which absorbs light having frequency between 320 nm and 900 nm, can form free radicals, is at least partially water soluble, and is non-toxic to the biological material at the concentration used for polymerization.

92. The method of claim 91 wherein the photoinitiator is selected from the group consisting of 2,2-dimethoxy,2-phenylacetophenone and 2-methoxy,2-phenylacetophenone.

93. The method of claim 81 wherein the macromer solution further comprises a cocatalyst and the photoinitiator is selected from the group consisting of ethyl eosin, eosin Y, fluorescein, 2,2-dimethoxy,2-phenylacetophenone, 2-methoxy,2-phenylacetophenone, camphorquinone, rose bengal, methylene blue, erythrosin, phloxime, thionine, riboflavin and methylene green.

94. The method of claim 93 wherein the cocatalyst is a nitrogen based compound capable of stimulating a free radical reaction.

95. The method of claim 93 wherein the cocatalyst is a nitrogen atom-containing electron-rich molecule.

96. The method of claim 93 wherein the cocatalyst is a primary, secondary, tertiary or quaternary amine.

97. The method of claim 96 wherein the cocatalyst is selected from the group consisting of triethanolamine, triethylamine, ethanolamine, N-methyl diethanolamine, N,N-dimethyl benzylamine, dibenzyl amine, N-benzyl ethanolamine, N-isopropyl benzylamine, tetramethyl ethylenediamine, potassium persulfate, tetramethyl ethylenediamine, lysine, ornithine, histidine and arginine.
98. The method of claim 81 wherein the radiation has a wavelength between 320 nm and 900 nm.
99. The method of claim 98 wherein the radiation has a wavelength between 350 nm and 700 nm.
100. The method of claim 81 wherein the macromer solution further comprises an accelerator to accelerate the rate of polymerization.
101. The method of claim 100 wherein the accelerator is a small molecule containing an allyl, vinyl or acrylate group)
102. The method of claim 101 wherein the accelerator is selected from the group consisting of N-vinyl pyrrolidinone, 2-vinyl pyridine, 1-vinyl imidazole, 9-vinyl carbazole, acrylic acid and 2-allyl,2-methyl,1-3-cyclopentane dione.
103. The method of claim 102 wherein the accelerator is N-vinyl pyrrolidinone.

104. The method of claim 81 wherein the biomedical device is a catheter.

105. The method of claim 81 wherein the biomedical device is a container enclosing mammalian tissue or cells.

106. The method of claim 81 wherein the biomedical device is tubing.

107. The method of claim 81 wherein the biomedical device is an ultrafiltration membrane.

108. A method for joining together two biological surfaces comprised of forming a water insoluble polymer between and adhering to each of the two surfaces comprising the steps of:

- (a) juxtaposing the two surfaces to be joined;
- (b) applying to the joint a macromer solution comprised of macromer and photoinitiator; and
- (c) polymerizing the macromer by exposing the macromer solution to light radiation.

109. The method of claim 108 wherein the macromer is a water soluble, ethylenically unsaturated, polymer susceptible to polymerization into an water insoluble polymer through interaction of at least two carbon-carbon double bonds.

110. The method of claim 109 wherein the macromer is selected from the group consisting of ethylenically unsaturated derivatives of poly(ethylene oxide) (PEO), poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP),

poly(ethyloxazoline) (PEOX), poly(amino acids), polysaccharides, and proteins.

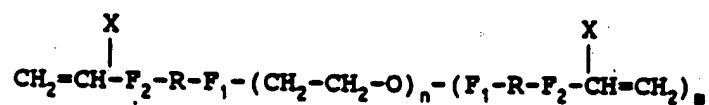
111. The method of claim 110 wherein the PEG is PEG multiacrylate.

112. The method of claim 111 wherein the PEG is PEG tetraacrylate which has a molecular weight around 18,500 D.

113. The method of claim 110 wherein the polysaccharides are selected from the group consisting of alginate, hyaluronic acid, chondroitin sulfate, dextran, dextran sulfate, heparin, heparin sulfate, heparan sulfate, chitosan, gellan gum, xanthan gum, guar gum, water soluble cellulose derivatives and carrageenan.

114. The method of claim 110 wherein the proteins are selected from the group consisting of gelatin, collagen and albumin.

115. The method of claim 108 wherein the macromer is of the formula



where $\text{F}_1 = \text{CONH}, \text{COO}$ or NHCOO

$\text{X} = \text{H}, \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5, \text{Cl}, \text{Br}, \text{OH}$ or CH_2COOH

$\text{F}_2 = \text{COO}, \text{CONH}, \text{O}$ or C_6H_5 ,

$\text{R} = \text{CH}_2$ or -alkyl-,

$n \geq 5$, and $m \geq 2$.

116. The method of claim 108 wherein the photoinitiator is any dye which absorbs light having frequency between 320 nm and 900 nm, can form free radicals, is at least partially water soluble, and is non-toxic to the biological material at the concentration used for polymerization.

117. The method of claim 116 wherein the photoinitiator is selected from the group consisting of 2,2-dimethoxy,2-phenylacetophenone and 2-methoxy,2-phenylacetophenone.

118. The method of claim 108 wherein the macromer solution further comprises a cocatalyst and the photoinitiator is selected from the group consisting of ethyl eosin, eosin Y, fluorescein, 2,2-dimethoxy,2-phenylacetophenone, 2-methoxy,2-phenylacetophenone, camphorquinone, rose bengal, methylene blue, erythrosin, phloxime, thionine, riboflavin and methylene green.

119. The method of claim 118 wherein the cocatalyst is a nitrogen based compound capable of stimulating a free radical reaction.

120. The method of claim 118 wherein the cocatalyst is a a nitrogen atom-containing electron-rich molecule.

121. The method of claim 118 wherein the cocatalyst is a primary, secondary, tertiary or quaternary amine

122. The method of claim 121 wherein the cocatalyst is selected from the group consisting of triethanolamine, triethylamine, ethanolamine, N-methyl diethanolamine, N,N-

dimethyl benzylamine, dibenzyl amine, N-benzyl ethanolamine, N-isopropyl benzylamine, tetramethyl ethylenediamine, potassium persulfate, tetramethyl ethylenediamine, lysine, ornithine, histidine and arginine.

123. The method of claim 108 wherein the radiation has a wavelength between 320 nm and 900 nm.

124. The method of claim 123 wherein the radiation has a wavelength between 350 nm and 700 nm.

125. The method of claim 108 wherein the macromer solution further comprises an accelerator to accelerate the rate of polymerization.

126. The method of claim 125 wherein the accelerator is a small molecule containing an allyl, vinyl or acrylate group.

127. The method of claim 126 wherein the accelerator is selected from the group consisting of N-vinyl pyrrolidinone, 2-vinyl pyridine, 1-vinyl imidazole, 9-vinyl carbazole, acrylic acid and 2-allyl,2-methyl,1-3-cyclopentane dione.

128. The method of claim 127 wherein the accelerator is N-vinyl pyrrolidinone.